

Q4 36. (Amended) The method according to Claim 1, which further comprises using the NT unit together with a fertilized embryo to produce a chimeric embryo.

41. (Amended) A method of producing a pluripotent porcine CICM cell line, comprising:

Q5 (i) inserting a desired differentiated pig cell or cell nucleus into an optionally enucleated pig oocyte, under conditions suitable for the formation of a nuclear transfer (NT) unit;

(ii) removing the endogenous oocyte nucleus if not already effected;

(iii) activating the resultant nuclear transfer unit;

(iv) culturing cells obtained from said activated NT unit to obtain a porcine CICM cell line which is pluripotent and may be maintained indefinitely in tissue culture.

REMARKS

This Reply is responsive to the Office Action dated December 6, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 C.F.R. § 1.112 is respectfully requested. In accordance with 37 C.F.R. § 1.121, the changes made in the first paragraph of the specification and in the claims by the following amendment are shown in the marked-up versions that are attached as an appendix.

Regarding the declaration:

After the present application was filed, two of the inventors, Steven Stice and Paul Golueke, refused to sign the declaration pursuant to 37 C.F.R. § 1.63. Accordingly, on April 6, 2000, Applicants filed a declaration of facts describing the situation, and a petition

requesting that the declaration be accepted without the signatures of all of the inventors, pursuant to 37 C.F.R. § 1.47(a). Please hold the objection to the declaration in abeyance while waiting for action to be taken on the petition 37 C.F.R. § 1.47(a).

Amendment of the Text of the Specification:

The first paragraph of the specification has been amended to identify the two U.S. patents that have issued from the parent applications, as called for in the Office Action.

Amendment of the Claims:

Claims 35, 38-40, 43, 45, and 48 are canceled, and claims 1, 30-32, 36, and 41 are amended in response to the Office Action.

Claim 1 is amended specify that the NT unit is transferred to a host female porcine for development into a porcine fetus or animal, support for which is found in the specification, for example, at line 10 of page 20.

Claims 30-32 are amended by deleting the word “fused,” for which there is no antecedent basis.

Claim 36 is amended by deleting the word “cloned” from the term “cloned NT unit,” and by re-wording the claim to recite “using the NT unit together with a fertilized embryo to produce a chimeric embryo,” support for which is found in the specification, for example, at lines 17-19 of page 16. Methods for producing chimeric animals by combining one or more cells of one embryo (e.g., a blastocyst) with a different, fertilized embryo to produce a chimeric pig were well known by those skilled in the art at the time the application was filed (see, for example, Inoue et al., Pigment Cell Research, 1996, 9(6):289-297, abstract attached). Support for the amended claim is also found in claim 18 of U.S. Patent No. 6,235,969, which

recites combining a cell of the NT unit with an embryo to produce a chimeric embryo, and which is incorporated into the present application by reference.

Claim 41 is amended for greater clarity by re-wording the recited "CICM (pluripotent) cell line" in line 1 and step (iv) of the claim as a "pluripotent porcine CICM-derived cell line," and also by changing the term "cultured NT unit" in step (iv) to "activated NT unit," for which there is antecedent basis in step (iii).

No new matter has been added by the above-described amendments.

Regarding Rejection of the Claims for Provisional Obviousness-type Double Patenting:

Claims of the application are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No.s 6,235,969 and 5,945,577. Applicants respectfully request that this rejection be held in abeyance until allowance is negotiated. At that time, if the claims in the instant application are still deemed to be obvious in view of the claims of the issued patents, Applicants will consider submitting a terminal disclaimer.

Rejection of claims under 35 U.S.C. §112, first paragraph:

The claims were rejected under 35 U.S.C. §112, first paragraph, because the specification is not considered to be enabling for the disclosed method for cloning a porcine fetus or offspring via nuclear transfer, in which (i) the recipient cell is a blastomere, (ii) there is no fusion step, or (iii) the donor cell or nucleus is transferred into a mammal other than a female porcine.

Claim 1 is amended to include the limitation that the donor cell or nucleus is transferred into a female porcine, in keeping with the description of the method for cloning a pig on page 20 of the specification. However, Applicants respectfully traverse the rejection

on the grounds that use of blastomeres as recipient cells is not enabled, and fusion is a necessary element of the claimed method.

With respect to using blastomeres, it appears that the significance of the 1992 report by Kato et al. cited by the Examiner has been misconstrued in the Office Action. Kato et al. state at the top of page 770 that “[i]t is not clear in mammals whether isolated germ cells have totipotency or pluripotency,” and the 1992 article describes using the method of nuclear transplantation in which a single germ cell is transplanted into one enucleated blastomere of a two-cell embryo in order to examine the pluripotency of mouse fetal germ cells. Kato et al. state in the paragraph at the top of page 770 that Nakamura et al. (1987) and Kono et al. (1989) have shown that chimeric mice are successfully produced by transplanting single nuclei of two- and eight-cell embryos into an enucleated blastomere of a two-cell embryo. Similar results are described in Kono et al. (J. Exp. Zool., 1991, 257(2): 214-219, abstract attached), which reports that identical twin and triplet mice are produced by transplantation of single nuclei from two- and four- cell embryos into one of the enucleated blastomeres of a two-cell embryo. Contrary to the suggestion by the Office Action that blastomeres are poor nuclear transfer recipient cells, Kato et al. used the blastomere assay because it successfully produces chimeric mice if the nuclear transplant donor cells are pluripotent. Kato et al. describe the failure of mouse fetal germ cells to produce chimeric mice as being attributable to incompatibilities between the donor fetal germ cells and the recipient blastomeres, rather than to the inability of blastomeres to serve as recipient cells (see the discussion in the last paragraph on page 777). The embryogenic potential of blastomeres is also shown by Johnson et al. (Vet. Rec., 1995, 137(1):15-16, abstract attached), who describe separating the blastomeres of a four-cell embryo, culturing them to form blastocysts, and implanting these into cows to produce four identical calves. Similarly, Niemann et al. (Theriogenology, 2001, 56(8): 1291-1304, abstract attached) report that individual blastomeres of porcine 4-cell and

8-cell embryos can be cultured in vitro to the blastocyst stage; and Chan et al. (Science, 2000, 287:317-319, abstract attached) report that blastomeres of primate embryos can be separated to produce identical twins and larger sets. Applicants respectfully contend that scientific articles such as the Kato et al. reference cited in the Office Action, and others, support the use of blastomeres as nuclear transplant recipient cells, as discussed above, and that one of skill in the art would be able to practice the claimed invention using blastomeres as nuclear transplant recipient cells, in accord with the teachings of the specification, without undue experimentation.

In regard to the requirement that claim 1 recite a fusion step, the Applicants note that the claimed method comprises transferring either a donor cell, or the nucleus of a donor cell, to a recipient oocyte or blastomere. A skilled practitioner would know that fusion would be called for only when the method is carried out by transferring an intact donor cell to a recipient cell, and that fusion would not necessary when the method is practiced by transferring the nucleus of a donor cell (e.g., as a lysed donor cell) to a recipient cell. The specification (page 1, lines 15-19) teaches that Collas et al. (1994) describe microinjection of nuclei of lysed bovine ICM cells into enucleated bovine oocytes to produce cloned bovines. One skilled in the art would recognize that similar techniques can be used successfully to produce cloned mammals of other species. For example, Ilmensee (Cell, 1981, 23:9-18, copy attached) describes microinjecting nuclei of murine cells into enucleated murine oocytes to produce cloned mice; and Onishi et al. (Science, 2000, 289:1188-1190, copy attached) describes microinjecting nuclei of porcine cells into enucleated porcine oocytes to produce a cloned piglet. Thus, one of skill in the art would know that some embodiments of the claimed method call for fusion, but that others do not. This appears to have been recognized by the U.S. Patent and Trademark Office in issuing the claims of U.S. Patent Nos. 5,945,577 and 6,235,969 in the parent applications. Like the present claims, the issued claims recite

cloning methods that comprise inserting either a donor cell, or the nucleus of such a cell, into a recipient cell, but do not include the step of fusion as a necessary claim element. For example, see claim 3 of U.S. Patent No. 5,945,577, and claim 1 of U.S. Patent No. 6,235,969. Requiring the claims of the present application to be limited to a method that uses fusion would unfairly deny the Applicants the scope of the claims to which they are entitled by the nature of their invention.

In view of the above, the Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections of claims under 35 U.S.C. §112, second paragraph:

Claims 30-32, 36, and 41-48 were rejected under 35 U.S.C. §112, second paragraph as being indefinite.

Claims 30-32 are amended by deleting the word “fused,” for which there is no antecedent basis.

Claim 36 is amended by deleting the word “cloned” from the term “cloned NT unit,” for which there is no antecedent basis.

Claim 41 is re-written so that it does not recite “pluripotent” as a parenthetical term, to give greater clarity.

The grounds for rejection raised under 35 U.S.C. §112, second paragraph have been addressed by the above amendments, and withdrawal of the rejection is respectfully requested.

Rejections of claims under 35 U.S.C. §102:

Product claims 35, 38-40, 43, and 48, that were rejected under 35 U.S.C. §102(a) or §102(e) as being anticipated by products disclosed by Wheeler, Fodor et al., Strojek et al., or Chang et al., have been canceled, so the rejection is moot.

All of the issues raised by the Office Action dated December 6, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,


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Date: June 6, 2002

APPENDIX

The changes in the specification and claims made by the amendment stated above are shown in the marked-up versions shown below:

IN THE SPECIFICATION:

The paragraph beginning at line 2 of page 1 is amended as shown below:

-- This application is a continuation-in-part of U.S. [Serial] Application No. 08/888,057, filed July 3, 1997, now U.S. Patent No. 6,235,969, which is a continuation-in-part of U.S. [Serial] Application No. 08/781,752, filed January 10, 1997, now U.S. Patent No. 5,945,577, the contents of which are hereby incorporated by reference. --

IN THE CLAIMS:

Claims 1, 30-32, 36, and 41 are amended as shown below.

1. (Amended) A method of cloning a porcine fetus or live offspring, comprising:
 - (i) inserting a desired differentiated pig cell or cell nucleus into an optionally enucleated pig oocyte or blastomere, under conditions suitable for the formation of a nuclear transfer (NT) unit;
 - (ii) removing the endogenous nucleus from said oocyte or blastomere if not previously removed;
 - (iii) activating the resultant nuclear transfer unit;
 - (iv) optionally culturing said NT unit; and

(v) transferring said optionally cultured NT unit to a host female porcine [mammal] such that the NT unit develops into a porcine fetus or animal.

30. (Amended) The method according to Claim 1, wherein the [fused] nuclear transfer unit is activated by exposure to a single or multiple electrical pulses.

31. (Amended) The method according to Claim 1, wherein the [fused] nuclear transfer unit is activated by exposure to ionomycin and DMAP.

32. (Amended) The method according to Claim 1, wherein the [fused] nuclear transfer unit is activated by exposure to at least one activating factor derived from sperm cells.

36. (Amended) The method according to Claim 1, which further comprises using [combining] the [cloned] NT unit together with a fertilized embryo to produce a chimeric embryo.

41. (Amended) A method of producing a pluripotent porcine CICM [(pluripotent)] cell line, comprising:

(i) inserting a desired differentiated pig cell or cell nucleus into an optionally enucleated pig oocyte, under conditions suitable for the formation of a nuclear transfer (NT) unit;

(ii) removing the endogenous oocyte nucleus if not already effected;

(iii) activating the resultant nuclear transfer unit;

(iv) culturing cells obtained from said [cultured] activated NT unit to obtain a [pig] porcine CICM cell line[,] which is pluripotent and may be maintained indefinitely in tissue culture.